Master's Thesis of Yeonkyung Cho

Epidemiology and Burden of Disease Associated with Short Bowel Syndrome in Korea

한국에서의 단장증후군 환자 역학과 질병부담

August 2017

Graduate School of Public Health

Seoul National University

Public Health Major

Yeonkyung Cho

Epidemiology and Burden of Disease Associated with Short Bowel Syndrome in Korea

Sungho Won

Submitting a master's thesis of Public Administration

May 2017

Graduate School of Public Health
Seoul National University
Public Health Major

Yeonkyung Cho

Confirming the master's thesis written by
Yeonkyung Cho

July 2017

Chair	Sungil Cho	(Seal)
Vice Chair	Wankyo Chung	(Seal)
Examiner	Sungho Won	(Seal)

Abstract

Epidemiology and Burden of Disease Associated with Short Bowel Syndrome in Korea

Yeonkyung Cho

Department of Public Health

Graduate School of Public Health

Seoul National University

Background/Objective: There is a lack of large database research relating to the epidemiology and burden of disease associated with short bowel syndrome (SBS) in South Korea. The aim of this study is to investigate the epidemiologic features of SBS and to assess the burden of SBS from the National Health Insurance Service–National Sample Cohort (NHIS-NSC) who had at least once SBS underlying disease in 2002-2013 for the first time in Korean population.

Method: This study analyzed the NHIS-NSC database, consisting of 1,025,340 participants who was randomly selected, comprising 2.2% of the total eligible Korean population in 2002, and followed for 12 years until 2013 unless participants' eligibility was disqualified due to death or emigration. Patients with SBS were operationally defined as three groups; definite/probable/possible SBS using combination of diagnostic code, operational code and hospitalization period. Prevalence and incidence estimation, co-morbidities analysis, survival analysis and cost estimation were conducted.

Results: A total of 344 individuals were identified as patients with SBS (219 possible SBS, 119 probable SBS, 6 definite SBS) among 47,406 patients who had at least once SBS underlying disease during the period of 2002-2013. The prevalence of SBS was about 2-3 per hundreds of thousands and its incidence rate was 0.135 per person-year. Kaplan-Meier survival curves show that all SBS groups were associated with the highest risk in the congenital disease group. In terms of medical and economic burden of disease

of SBS, data confirmed that SBS in Korea imposes a substantial medical and economic burden. When categorized according to health care institution, the proportion of total SBS patients in primary clinics was 6.1% and that in referral centers, defined as general hospitals plus hospitals, was 90.9% and that in convalescent hospitals was 3.0%. The mean (±standard deviation) length of stay in clinics for any of outpatients and admission was 6.1 ± 13.2 days per year and that in hospitals was 63.1 ± 139.6 days. The mean (±standard deviation) length of stay in general hospitals was 80.2 ± 85.8 days per year and that in convalescent hospitals was the longest, 200.0 ± 401.9 days per year which means patients who are in convalescent hospitals spend more than half of year in hospitals.

Conclusion: The SBS is ultra-rare disease but give experience of complicated inpatient courses related to their disease as well as high economic burden of disease. This study represents the first use of national health claims data to study the epidemiology and burden of disease associated with SBS.

Keywords : Short Bowel Syndrome, Epidemiology, Burden of Disease, Korea

Student Number **: 2015-24017**

Contents

Lists of Tables

Lists of Figures

Ⅰ. Introduction

1. Background & Necessity

Short bowel syndrome (SBS) is an ultra-rare [1], serious, disabling, socially incapacitating and potentially life-threatening condition (Nightingale, 2006). SBS results from surgical resection, congenital defect, or disease-associated with loss of intestinal absorptive capacity (O'Keefe, et al., 2006). SBS typically follows major surgical resection of the small intestine due to various underlying diseases such as recurrent Crohn's disease, mesenteric ischemia, radiation enteritis, trauma, volvulus, malignancy, and complications from previous abdominal surgery in adults, whereas children are mainly affected by intestinal volvulus, intestinal malformations and necrotizing enterocolitis (Bakker, et al., 1999; Donohoe & Reynolds, 2010; DiBaise, et al., 2004; Wales, et al., 2004; Thompson, et al., 2011; Pironi, et al., 2006; Jeppesen, et al., 2014).

As a result, SBS patients have a reduced absorption of macronutrients, water and electrolytes, and are at risk for malnutrition, diarrhea, dehydration and weight loss (O'Keefe, et al., 2006; Sundaram, et al., 2002). When nutritional requirements cannot be met by oral or enteral intake, parenteral support (PS) is needed to compensate the loss of intestinal function and to prevent fatal consequences associated with dehydration and/or malnutrition.

Length of intestine by itself does not define SBS. SBS is best defined by the

---

[1] Rare and ultra-rare diseases affect very small numbers of patients. In the UK, a disease is defined as rare if it affects fewer than 5 persons per 10,000 population (Official Journal of the European Communities, 1999; Official Journal of the European Union, 2011). A disease is generally considered to be ultra-rare if it affects fewer than 1 in 100,000 population (EUCERD, 2013) [or 1 in 50,000 population] in the UK (EMINET, 2011).

functionality of both the small intestine and colon, independent of remaining anatomic length. A small bowel length of 100–120 cm without a colon, or 50 cm of small bowel with a colon have also been used to define SBS. The clinically relevant definition of SBS is inadequate functional bowel to support nutrient and fluid requirements for that individual, regardless of the absolute length of the GI tract (Parrish, 2005).

Intestinal failure results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance (O'Keefe, et al., 2006). Therefore, SBS represents a subset of patients with intestinal failure.

The epidemiology of SBS is not well known, in part due to the rarity of the disease, patient heterogeneity, inconsistent disease definition used in studies, inconsistent bowel measurement and lack of SBS patients registries (Buchman, 2006; Jeppesen, 2014).

The prevalence and incidence of home parenteral nutrition (HPN) dependent patients are often used as a proxy indicator of SBS, as HPN is the standard of care for SBS patients who are unable to maintain their nutritional/fluid/electrolyte balance through oral nutrition only (Bakker, et al., 1999; Messing, et al., 1998; Keller, et al., 2004). European surveys of home PN indicated an incidence of 2-3 patients per million and a prevalence of 4 per million (Bakker, et al., 1999; Van Gossum, et al., 1996). The annual prevalence of home PN in the United States was approximately 120 per million population, of whom about 25 percent have SBS; this amounted to about 10,000 individuals in 1992 (Howard, et al., 1995). In US study of over 12,000 infants, the incidence of surgery-induced SBS was 0.7% (7/1000) (Cole, et al., 2008)

The Canadian Collaborative Study Group estimated the incidence of SBS across Canada as 4.8/million population/year, but the calculation was based on a sample size of

only 11 infants. Another single population-based study, Canadian study used administrative health care data and federal census data within a defined catchment area to determine estimates. The incidence of neonatal SBS was found to be 24.5 per 100,000 live births (95% confidence interval (CI) = 12.1, 36.9) with a much higher incidence in infants born before 37-week gestation compared with term newborns (353.7/100,000 live births vs 3.5/100,000 live births) (CAPS, 1999).

Orphanet, the European portal for rare diseases and orphan drugs, provides an estimation for the overall SBS prevalence in Europe of 34 cases per million as of June 2013. This figure is higher than prevalence obtained from adult HPN data, as it includes all pediatric and adult cases from both congenital and surgical origin, and there is no clear definition of SBS. However, as highlighted in the Orphanet report, it is likely to be an overestimation of the actual SBS prevalence, as it is the mean of the highest and lowest values collected in the very few published European literature. Those studies are usually done in regions of higher prevalence and / or based on hospital data (Orphanet, 2013).

SBS is associated with significant morbidity and mortality. Patients with SBS are highly prone to maintain chronic PS to compensate for the loss of intestinal function and to prevent fatal consequences associated with dehydration and/or malnutrition. Although PS can meet basic nutrition and fluid requirements, it is associated with shortened life span, life-threatening infectious and metabolic complications, and reduced quality of life (Hartl, et al., 2009). The development of PS-associated liver disease predisposes patients to sepsis, irreversible liver damage, metabolic bone disease, and increased mortality risk (Thompson, et al., 2011). While the overall survival of SBS at 10 years following resection is 52%, patients who remain PS-dependent long-term have a poorer 10-year survival rate (40.7%) than those who can be weaned off PS (67%) (Amiot, et al., 2013).

Although SBS is an orphan disease, the condition poses a considerable economic burden on patients and payers, as in most cases it requires lifelong management with expensive therapy, associated with substantial direct and indirect costs related to complications management, multiple hospitalizations, and patient unemployment (Schalamon, et al., 2003; Van Gossum, et al., 2001; Pironi & Tognoni, 1995; Staun, et al., 2007).

Despite of high burden of disease, unfortunately, few data derived from large database research are available regarding the epidemiology and burden of disease associated with short bowel syndrome. Previous studies were restricted to either single center or relatively small multicenter collaborations (Nusinovich, et al., 2013; Sanchez, et al., 2013). These data are thus unable to accurately portray the national disease burden and likely underrepresent the full disease impact carried by SBS.

In this study, I focus one of the largest representative health claim databases, the National Health Insurance Service–National Sample Cohort (NHIS-NSC). The NHIS-NSC is a population-based cohort established by the National Health Insurance Service (NHIS) in South Korea. This cohort consists of 1,025,340 participants who was randomly selected, comprising 2.2% of the total eligible Korean population in 2002, and followed for 11 years until 2013 unless participants' eligibility was disqualified due to death or emigration. Thus general conclusion regarding epidemiology and burden of disease with short bowel syndrome in South Korea can be obtained and hope to aid in future research and healthcare planning relating to these patients.

2. Objectives

The aim of this study is to investigate the epidemiologic features of SBS and to assess the SBS burden from the NHIS cohort who had at least once SBS underlying disease in

2002-2013 for the first time in Korean population. In particular, this study will estimate the prevalence and incidence of SBS and compare the incidence and hazard ratio of SBS by type of underlying disease because SBS has various etiologic features. Accurate estimates of SBS prevalence and incidence are difficult to determine due to the rarity of the condition, variation in the definition of SBS between institutions, difficulty of tertiary care referral centers to accurately determine their catchment population and problems ensuring complete follow-up of the cohort. But the NHIS cohort were selected using systematically stratified random sampling with proportional allocation within each stratum based on the individual's total annual medical expenses and followed up for 11 years. Thus this results could be imposed the whole Korean population. In addition, this study will investigate frequent diagnosis code accompanying SBS and estimate the medical and socioeconomic burdens of SBS. To summarize, the main goal of this study is to figure out the current status of SBS in South Korea using real world data for the future healthcare decision making related to the rare disease because there are no published data regarding epidemiology of SBS in Korea.

The detail purposes of this study are as follows:

1. To estimate the prevalence and incidence of SBS in NHIS's 2002-2013 cohort with SBS underlying disease
2. To assess the incidence and hazard ratio of SBS by type of underlying disease
3. To identify frequent co-morbidity of SBS
4. To estimate the medical and socioeconomic burdens of SBS

Ⅱ. Method

The study protocol was approved by the Institutional Review Board of the Seoul National University (IRB No. E1703/002-003) and National Health Insurance Service (NHIS-2017-2-334) for the usage of the cohort database.

1. Data source and dataset configuration

This cohort study used the NHIS sample cohort, having randomly selected 1,025,340 participants in 2002 comprising 2.2% of the total eligible Korean population, following for 11 years until 2013 unless participants' eligibility was disqualified due to death or emigration. During the follow-up period, the cohort was refreshed annually by adding a representative sample of newborns, sampled across 82 strata (two for sex, combined with 41 for parents' income levels) using the 2.2% sampling rate.

The cohort comprises four databases on participants' insurance eligibility, medical treatments, medical care institutions and general health examinations. The insurance eligibility database (Table JK) contains 14 variables including information on participant's identity and socioeconomic variables such as gender, residential area, type of health insurance, level of income, type and grade of disability registered, birth and death. The medical treatment database consists of 57 variables containing information about participants' medical bills claimed by medical service providers. It comprises four databases: participant's electronic medical treatment bills (Table 20), bill details (Table 30), details of diseases (Table 40) and details of prescriptions (Table 60). All four databases are further classified according to type of medicine: 'medical' and 'dental& Chinese medicine' tables. A pharmacy table is also included in the first two databases. In the medical care institution database, information regarding the type of institution,

establishment, location, number of beds, facilities and physicians are recorded under 10 variables. The general health examination database comprises information regarding nationwide health examinations conducted by the NHIS in 2002–13, including major health examination results and information about lifestyles and behaviors obtained from questionnaires.

In this study, data of patients who had at least once SBS underlying disease from 2002 to 2013 are starting point for data construction. Thus all annual tables of each database (Table JK, Table 20, Table 30, Table 40) were combined to one table from 2002 to 2013 and the diagnosis KCD codes for SBS underlying disease were extracted from the data in Table 40. The KCD codes for SBS underlying disease can be found in Table 1. There were 4 versions of KCD code used from 2002 to 2013 but no KCD codes of SBS underlying disease were updated (Enforcement date: KCD-3 1995.01.01, KCD-4 2003.01.01, KCD-5 2008.01.01, KCD-6 2011.01.01). The table 40 only has sequence key (key_seq) which substituted to the billing statement identification code thus they were merged with Table 20 which has the data of the patients' ID by matching sequence key. Afterwards Table 30 which has operation code and admission period were merged by matching patients' ID. Finally, they were merged by patients' ID with Table JK for the data of demographic factors. By merging in the same order as above, it is possible to identify missing values at the beginning of the merging phase and reduce the resources used for the analysis. The missing values were defined as the absence of information about sex. In addition, even though the patient had both underlying disease KCD code and operation code or SBS KCD code, if underlying disease KCD code was received later, the patient was defined as missing value. Final study cohort comprised 47,406 patients who has underlying disease of SBS at least once during the period. The pipeline for the dataset configuration is shown in the following Figure 1.

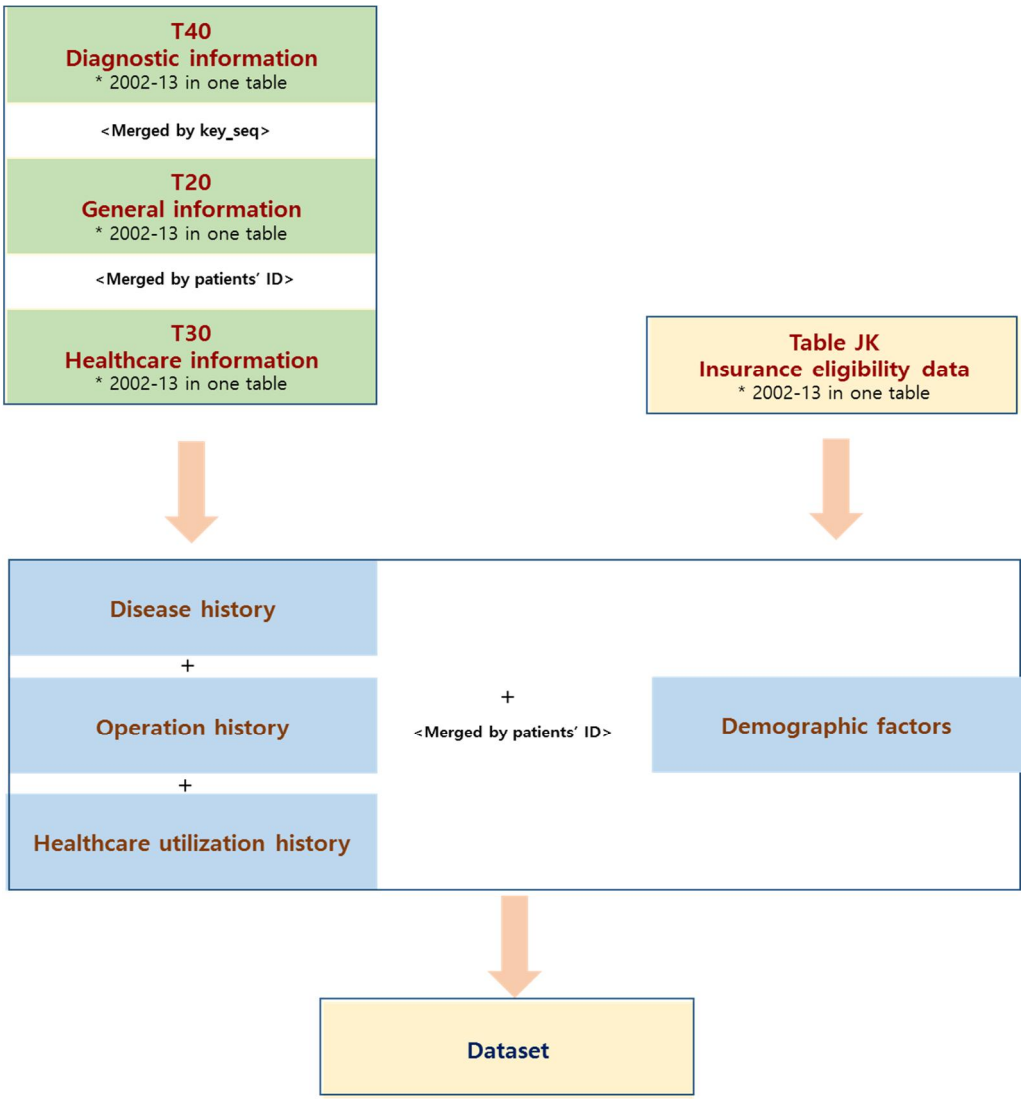

Figure 1 The pipeline for the dataset configuration

2. Variable Definition

SBS may be defined either anatomically - based on a percentage of bowel length remaining; or functionally - as insufficient bowel to provide the necessary fluid and

nutrient absorption to sustain life and growth. The remaining bowel length was not provided in the claims data thus here subjects were considered as SBS patients if they satisfy the following requirements:

1) Definite Short Bowel Syndrome (meet all four criteria)
    - ✓ Having SBS diagnostic code: K918 (Short bowel syndrome) or K912 (Postsurgical malabsorption)
    - ✓ Admission more than 6 weeks after intestinal resection
    - ✓ Having diagnostic code of underlying disease for SBS
    - ✓ Having operational code related to intestinal resection
2) Probable Short Bowel Syndrome (meet all three criteria)
    - ✓ Admission more than 6 weeks after intestinal resection
    - ✓ Having diagnostic code of underlying disease for SBS
    - ✓ Having operational code related to intestinal resection
3) Possible Short Bowel Syndrome (meet both criteria)
    - ✓ Having diagnostic code of underlying disease for SBS
    - ✓ Having operational code related to intestinal resection

Patients with SBS were identified as those who had at least once medical claim with any diagnostic codes based the physician's diagnosis. However most SBS patients could have more than one disease at the same time thus identifying SBS cases solely based on diagnostic code can cause misclassification problems due to potential miscoding. The primary feature of SBS is intestinal resection and requirement of parenteral nutrition.

Because there are numbers of nutrition agents and no consistent guideline in South Korea for the usage of nutrition agents for patients with SBS, admission in hospital more than 6 weeks afterwards intestinal resection regards parenteral nutrition requirement. Also for finding more suitable patients, one criteria were added; having diagnostic code of underlying disease for SBS. Overall, definite SBS case was defined as those who had fulfilled all of above criteria.

Because SBS is ultra-rare disease and this is first trial for cohort based study, it seems meaningful to figure out the data of any suspicious SBS cases. Thus I categorized SBS cases as three; Definite SBS if meeting all four criteria, Probable SBS if only missing SBS diagnostic code among criteria, Possible SBS if having diagnostic code of underlying disease for SBS as well as intestinal resection. There were no exclusion criteria but even though patient had both underlying disease KCD code and operation code or SBS KCD code, if underlying disease KCD code was received later, the patient was excluded from the dataset. This study included SBS patients from the date of having diagnostic code of underlying disease for SBS. The List of diagnostic KCD code of underlying disease for SBS and operational code related to intestinal resection are shown in the following Table 1 and Table 2.

Table 1 List of KCD code of underlying disease for SBS

Disease	KCD code
Crohn's disease	K500, K501, K508, K509
Ulcerative colitis	K510
Radiation enteritis	K520, K521
Intestinal ischemia	K550, K551, K558, K559
Intussusception	K561
Volvulus	K562
Intestinal obstruction	K565, K566, K567

Diverticular disease of intestine	K570, K572, K574, K578
Perforation of intestine (nontraumatic)	K631
Fistula of intestine	K632
Ulcer of intestine	K633
Peritonitis	K650, K658, K659
Other disorders of peritoneum	K660, K661
Trauma	S364, S365, S367, S368, S399
Necrotizing enterocolitis	P77, P780, P781
Intestinal atresia	Q410, Q411, Q412, Q418, Q419, Q428, Q429
Agangionosis	Q431
Intestinal malrotation	Q433, Q434, Q438, Q439, Q458, Q459
Omphlaocele	Q792

Table 2 List of operational code related to intestinal resection

KCD code	Intestinal resection types
Q2571	Gastroduodenostomy
Q2572	Gastrojejunostomy
Q2573	Roux-En-Y Gastrojejunostomy,
Q2601	Esophagojejunostomy
Q2645	Polypectomy Of Small Bowel Or Colon
Q2650	Resection Of Small Intestine
Q2655	Diverticulectomy
Q2671	Right Or Left Hemicolectomy
Q1262	Colectomy-Subtotal
Q2672	Colectomy-Total
Q2673	Colectomy-Segmental Resection
Q2679	Colectomy With Proximal Colostomy And Distal Stump
Q2680	Intestinal Anastomosis
Q2676	Operation For Congenital Megacolon (Myomectomy)
Q2687	Operation For Congenital Megacolon (Radical)-Segmental Colonic Aganglionosis Type
Q2688	Operation For Congenital Megacolon (Radical)-Total Colonic Aganglionosis Type
Q2691	Operation For Intestinal Obstruction- Including Resection Of Intestine
Q2692	Operation For Intestinal Obstruction- Entero-Enterostomy

Q2693	Operation For Intestinal Obstruction-Adhesiolysis
Q2710	Intestinal Plication
Q2721	Operation Of Umbilical Hernia- With Resection Of Intestine
Q2761	Excision Of Mesenteric Tumor-With Resection Of Intestine
Q2771	Repair Of Bowel And Mesenteric Injury-With Resection Of Intestine
Q2831	Operation Of Congenital Intestinal Atresia- Simple Reconstruction
Q2832	Operation Of Congenital Intestinal Atresia-Complex
Q2841	Operation Of Midgut Malrotation-Ladd Procedure
Q2842	Operation Of Midgut Malrotation-Bowel Resection
Q2901	Ileal Pouch-Anal Anastomosis

3. Associated and Outcome Variables

There were lots of underlying disease of SBS thus for the analysis of incidence and hazard ratio of SBS by type of underlying disease, I categorized underlying disease as seven; 1) Inflammatory bowel disease: Crohn's disease and ulcerative colitis, 2) Radiation enteritis, 3) Intestinal ischemia, 4) Intestinal obstruction: intussusception, volvulus and intestinal obstruction, 5) Other diseases of intestine: Diverticular disease of intestine, perforation of intestine (nontraumatic), fistula of intestine, ulcer of intestine, peritonitis and other disorders of peritoneum, 6) Trauma, 7) Congenital: Necrotizing enterocolitis, intestinal atresia, agangionosis, intestinal malrotation and omphlaocele.

Death reason were derived from the database, which is from Statistics Korea. Death reason was classified by KCD codes.

Also I determined the most frequently associated KCD codes based on the physician's diagnosis codes to identify frequent co-morbidities of SBS. Specifically, I extracted KCD diagnoses codes that occurred at a frequency ≥1% in patients with SBS. All diagnostic codes in Table 40 were included which means it doesn't matter whether

recorded as a major primary code or the first four minor diagnostic codes. All the diagnostic codes that occurred before onset of SBS were excluded. Multiple co-morbidities were not mutually exclusive.

For the estimation of the medical and socioeconomic burdens of SBS, the outcome variables evaluated in this study were the number of SBS patients by type of healthcare institute, hospital length of stay and costs. Because of limitation of observational period, here the costs of SBS were defined only as direct costs, comprised of healthcare and pharmacy costs expended during two years after intestinal resection based on hypothesis that the medication costs were highest in the first two years after operation. If patients were dead before being two years after intestinal resection, the costs expended until the death were calculated. On average, death date from the operation date among dead SBS patients was 448 days which between one and two years after resection meaning medication will focus on first two years after operation. Healthcare costs were defined as the total expended costs which the medical care institution expended for the patients covered by medical insurance. It is composed of two kinds of costs, i.e. one burdened by Insurer and the by beneficiary. All the costs calculated in here was the cost finally adjusted by review, against the not-adjusted one estimated by medical care institution. Both costs were retrieved directly from the database. Healthcare institutions were classified into primary clinics, secondary care hospitals, and general hospitals and convalescent hospitals.

4. Statistical methods

Frequency analysis, prevalence and incidence estimation, and survival analysis were conducted. Frequency analysis was carried out to estimate the distributions of basic demographic variables such as gender, age and type of underlying disease based on the

year that firstly underlying disease occurred in 2002-2013 and to confirm the frequent co- morbidities of SBS in South Korea. In the NHIS cohort data, only age group by 5 ages, not the exact age was provided because of privacy protection. Thus if the patients were having the JK table in the year which patients firstly having SBS underlying disease diagnostic codes, then its age group was accepted. Otherwise the median age of age group in 2002 was applied. Also descriptive statistics were calculated based on variables such as medical utilization and cost measures, including numbers of patients, hospital length of stay, and healthcare services and pharmacy claims. The prevalence of patients with possible, probable and definite SBS was calculated per million. The incidence rate was calculated on the basis of person-year, and their 95% CIs were estimated by assuming Poisson distribution for disease occurrence. Time to SBS onsets from the point of underlying disease occurrence was analyzed with the crude Kapan-Meier curve analysis, which is a method of estimating the survival function by type of underlying disease until the SBS incidence respectively. If SBS patients were dead during observational period, death reasons were analyzed. Statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

Ⅲ. Results

1. Characteristics of study population

There are 1,113,656 subjects available in the cohort data of NHIS and subjects who satisfy the operational definition of SBS used in this study were included to the study population. The subjects were included or excluded following steps: Firstly, individuals who had not have at least once medical claim with any diagnostic codes of SBS underlying disease from 2002 to 2013 were excluded. Then subjects whose receiving intestinal resection before having the KCD codes of SBS underlying disease were removed. This population is total population including non-SBS patients and if satisfying the operational definition of SBS remains as study population with SBS. Figure 2 shows the summary for subject filtering described so far.

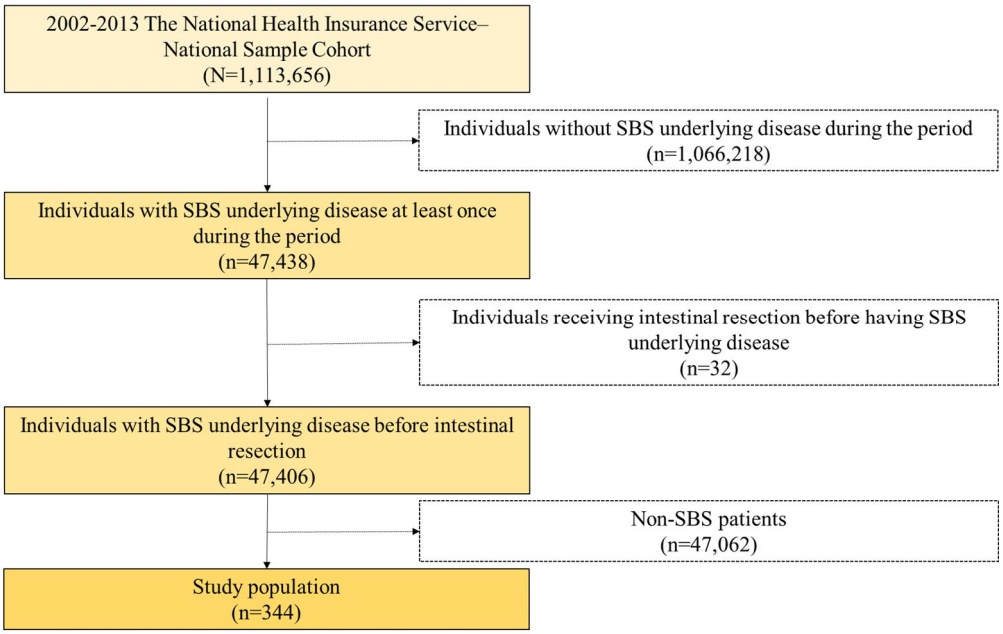

Figure 2 Procedure of data preparation

Study population consisted of 47,406 patients who had at least once diagnostic codes of SBS underlying disease during the period of 2002-2013. Among them, there were 219 patients with possible SBS, 119 patients with probable SBS and 6 patients with definite SBS as a total of 344 patients with SBS. The year of 2002 were the most frequent year which possible SBS patients firstly having SBS underlying disease diagnostic codes (n=28), followed by 2008 (n=25), 2007 (n=24), 2011 (n=23) and 2006 (n=22). For the probable SBS patients, the year of 2006 were the most frequent year (n=15) followed by 2003 (n=14), 2007 (n=13), 2010 (n=12) and 2002, 2004 (n=10, respectively). Definite SBS patients were only 6 and half of them were in 2009 (n=3). 58.7% of any SBS patients were male and 41.2% of them were females. The age group by 5 years old of patients by type of SBS was identified by frequency according to operational application mentioned in the statistical analysis method. The percentage of frequency in the age of 0 and age from 55 to 79 were slightly higher in the SBS patients compared to non-SBS patients. The type of underlying disease was divided by seven as mentioned in outcome variables definition. The most frequent underlying disease type among SBS patients was intestinal obstruction (45.6%), followed by other peritonitis, i.e. diverticular disease of intestine, perforation of intestine (nontraumatic), fistula of intestine, ulcer of intestine, peritonitis and other disorders of peritoneum (32.3%). The frequency and percentage of the above-mentioned variables by type of SBS are shown in Table 3.

Table 3 Characteristics of SBS patients in Korea in the NHIS

	Possible SBS	Probable SBS	Definite SBS	Total SBS	non-SBS	Total
	n	n	n	n (%)	n (%)	n (%)
Year of underlying disease						
2002	28	10	1	39	3,615	3,654
2003	16	14	0	30	3,680	3,710
2004	12	10	1	23	3,839	3,862
2005	16	7	0	23	3,890	3,913
2006	22	15	1	38	3,563	3,601
2007	24	13	0	37	4,053	4,090
2008	25	7	0	32	3,994	4,026
2009	9	7	3	19	4,079	4,098
2010	15	12	0	27	4,000	4,027
2011	23	9	0	32	4,421	4,453
2012	19	8	0	27	4,082	4,109
2013	10	7	0	17	3,846	3,863
Total	219	119	6	344	47,062	47,406
Demographics						
Sex						
Male	131	68	3	202 (58.7)	22,972	23,174 (48.9)
Female	88	51	3	142 (41.3)	24,087	24,229 (51.1)
Age group						
0	15	5	0	20 (5.8)	698 (1.5)	718
1~4	4	6	0	10 (2.9)	3,998 (8.5)	4,008
5~9	1	0	0	1 (0.3)	2,373 (5.0)	2,374
10~14	1	0	0	1 (0.3)	1,972 (4.2)	1,973
15-~19	1	1	0	2 (0.6)	2,116 (4.5)	2,118
20~24	4	2	0	6 (1.7)	2,353 (5.0)	2,359
25~29	8	4	1	13 (3.8)	2,774 (5.9)	2,787
30~34	7	1	0	8 (2.3)	2,977 (6.3)	2,985
35~39	6	3	0	9 (2.6)	2,995 (6.4)	3,004
40~44	10	8	0	18 (5.2)	3,087 (6.6)	3,105

45~49	13	7	0	20 (5.8)	3,339 (7.1)	3,359
50~54	16	11	0	27 (7.8)	3,295 (7.0)	3,322
55~59	22	13	0	35 (10.2)	2,865 (6.1)	2,900
60~64	21	15	1	37 (10.8)	2,864 (6.1)	2,901
65~69	27	17	3	47 (13.7)	2,766 (5.9)	2,813
70~74	30	13	0	43 (12.5)	2,495 (5.3)	2,538
75~79	17	10	1	28 (8.1)	1,944 (4.1)	1,972
80~85	12	1	0	13 (3.8)	1,294 (2.7)	1,307
85+	4	2	0	6 (1.7)	854 (1.8)	860
Underlying disease						
IBD	9	3	1	13 (3.8)	4,421 (9.4)	4,434 (9.4)
Radiation enteritis	3	2	0	5 (1.5)	9,375 (19.9)	9,380 (19.8)
Intestinal ischemia	12	7	1	20 (5.8)	2,322 (4.9)	2,342 (4.9)
Intestinal obstruction	103	50	4	157 (45.6)	19,297 (41.0)	19,454 (41.0)
Other peritonitis	68	43	0	111 (32.3)	9,929 (21.1)	10,040 (21.2)
Congenital	7	9	0	16 (4.7)	1,294 (2.7)	1,310 (2.8)
Trauma	17	5	0	22(6.4)	424 (0.9)	446 (1.0)

2. Prevalence and Incidence rate of Short Bowel Syndrome

Prevalence and incidence of SBS were estimated in order to examine the overall status of SBS in the period from 2002 to 2013. The prevalence was calculated by setting the year of SBS acquisition and by type of SBS. The prevalence of total SBS from 2002 to 2013 was about 2-3 per hundred thousand and among them, the prevalence of possible SBS was higher compared to other type of SBS, about 2 per hundred thousand. The prevalence of probable SBS was about 1 per hundred thousand and definite SBS prevalence was about 0.1 per hundred thousand.

The incidence of SBS was determined by setting the person-year. The overall

incidence of SBS was estimated to be 0.00135 person-year and the incidence of possible SBS was 0.00085. The incidence of probable SBS was 0.000465 and definite SBS incidence was 0.002344. More information on prevalence and incidence rate can be found from Table 4 and Table 5.

Table 4 Prevalence of SBS between 2002 and 2013 by SBS category

	Prevalence*			
	Possible SBS	Probable SBS	Definite SBS	Total
2002	1.268	0.683	0.000	1.951
2003	0.983	1.179	0.098	2.261
2004	1.574	0.787	0.000	2.361
2005	1.180	0.590	0.000	1.770
2006	2.894	1.397	0.100	4.391
2007	2.253	1.470	0.098	3.821
2008	1.899	0.600	0.000	2.498
2009	1.402	0.601	0.200	2.203
2010	1.896	1.397	0.000	3.293
2011	2.683	0.994	0.099	3.776
2012	2.274	1.088	0.000	3.362
2013	1.379	0.985	0.000	2.364

* per hundred thousand

Table 5 Incidence rate of SBS by SBS category

	The number of event	Incidence rate*
SBS		

Total	344	0.001350657
Possible SBS	219	0.00085835
Probable SBS	119	0.000465641
Definite SBS	6	0.002344144

* person-year

3. Kaplan-Meier curve of Short Bowel Syndrome by underlying disease

As mentioned in the method, the Kaplan-Meier curves were generated to see the time to SBS onsets from the point of underlying disease occurrence by type of underlying disease. Because of small SBS population, all the survival probability was similar to 1.0. However, both possible and probable SBS as well as total SBS were found to occur more frequently in subjects with congenital SBS underlying disease. The log-rank test was significant for all type of SBS including total SBS. To improve readability, number of subjects at risk is shown in below table instead of Kaplan-Meier curve.

Table 6 Number of Subjects At Risk Associated With Total Short Bowel Syndrome

Type of underlying disease	Days								
	0	500	1000	1500	2000	2500	3000	3500	4000
1	4,433	4,098	3,751	3,405	3,086	2,668	2,213	1,611	807
2	9,375	8,566	7,471	6,283	5,064	3,880	2,948	1,851	914
3	2,312	1,834	1,496	1,216	982	770	587	374	184
4	19,328	16,174	13,652	11,206	8,887	6,751	4,802	2,836	1,083
5	9,829	7,624	6,003	4,747	3,602	2,505	1,736	994	363
6	1,282	1,081	917	751	562	417	293	154	59
7	446	369	312	269	231	187	134	85	39

Table 7 Number of Subjects At Risk Associated With Probable Short Bowel Syndrome

Type of underlying disease	Days								
	0	500	1000	1500	2000	2500	3000	3500	4000
1	4,433	4,101	3,755	3,410	3,091	2,672	2,218	1,617	812
2	9,375	8,567	7,473	6,284	5,065	3,881	2,949	1,852	914
3	2,312	1,842	1,501	1,221	984	772	589	375	184
4	19,328	16,238	13,703	11,250	8,923	6,780	4,821	2,852	1,088
5	9,829	7,663	6,030	4,766	3,618	2,515	1,742	999	367
6	1,282	1,087	922	757	567	422	295	156	60
7	446	385	326	283	242	194	139	90	42

Table 8 Number of Subjects At Risk Associated With Possible Short Bowel Syndrome

Type of underlying disease	Days								
	0	500	1000	1500	2000	2500	3000	3500	4000
1	4,433	4,100	3,753	3,407	3,087	2,669	2,214	1,612	808
2	9,375	8,566	7,471	6,283	5,064	3,880	2,948	1,852	915
3	2,312	1,840	1,500	1,219	984	772	588	374	184
4	19,328	16,200	13,674	11,227	8,904	6,765	4,811	2,841	1,085
5	9,829	7,655	6,029	4,765	3,615	2,514	1,741	998	365
6	1,282	1,086	922	755	565	421	296	157	59
7	446	371	313	270	232	188	135	86	39

Table 9 Number of Subjects At Risk Associated With Definite Short Bowel Syndrome

Type of underlying disease	Days								
	0	500	1000	1500	2000	2500	3000	3500	4000
1	4,433	4,101	3,755	3,410	3,090	2,671	2,217	1,616	811
2	9,375	8,567	7,473	6,283	5,064	3,880	2,948	1,852	915
3	2,312	1,840	1,500	1,219	984	772	588	374	184
4	19,328	16,262	13,721	11,265	8,938	6,792	4,828	2,855	1,090
5	9,829	7,694	6,056	4,784	3,631	2,524	1,747	1,003	369
6	1,282	1,092	927	761	570	426	298	159	60
7	446	387	327	284	243	195	140	91	42

Also death reason of SBS patients if they were dead during study period were analyzed. Death reason were derived from our database originated from Statistics Korea Death Database. Among 344 SBS patients, 105 patients had died during observational period. Among the 105 death reasons, malignant neoplasm of stomach (C16) was the most frequent reason (17.14%), followed by malignant neoplasm of colon (C18). Sum of death because of malignant neoplasm of any organs was 66.62%, exceeded the half. The details were shown in Table 10.

Table 10 Death Reason of Short Bowel Syndrome patients during observational period

Code	Description	Possible SBS		Probable SBS		Definite SBS		Total	
		n	(%)	n	(%)	n	(%)	n	(%)
C16	Malignant neoplasm of stomach	11	16.92	6	15.38	1	100.00	18	17.14
C17	Malignant neoplasm of small intestine	1	1.54	1	2.56	0	0.00	2	1.9
C18	Malignant neoplasm of colon	9	13.85	8	20.51	0	0.00	17	16.19
C20	Malignant neoplasm of rectum	4	6.15	6	15.38	0	0.00	10	9.52
C22	Malignant neoplasm of liver and intrahepatic bile ducts	0	0.00	1	2.56	0	0.00	1	0.95
C24	Malignant neoplasm of other and unspecified parts of biliary tract	0	0.00	1	2.56	0	0.00	1	0.95
C25	Malignant neoplasm of pancreas	2	3.08	0	0.00	0	0.00	2	1.9
C26	Malignant neoplasm of other and ill-defined digestive organs	1	1.54	0	0.00	0	0.00	1	0.95
C34	Malignant neoplasm of bronchus and lung	2	3.08	0	0.00	0	0.00	2	1.9
C53	Malignant neoplasm of cervix uteri	0	0.00	2	5.13	0	0.00	2	1.9
C54	Malignant neoplasm of corpus uteri	0	0.00	1	2.56	0	0.00	1	0.95
C56	Malignant neoplasm of ovary	3	4.62	1	2.56	0	0.00	4	3.81
C57	Malignant neoplasm of other and unspecified female genital organs	1	1.54	0	0.00	0	0.00	1	0.95

C64	Malignant neoplasm of kidney, except renal pelvis	1	1.54	0	0.00	0	0.00	1	0.95
C67	Malignant neoplasm of bladder	2	3.08	1	2.56	0	0.00	3	2.86
C83	Non-follicular lymphoma	2	3.08	0	0.00	0	0.00	2	1.9
C84	Mature T/NK-cell lymphomas	1	1.54	1	2.56	0	0.00	2	1.9
E14	Unspecified diabetes mellitus	1	1.54	0	0.00	0	0.00	1	0.95
G40	Epilepsy	2	3.08	0	0.00	0	0.00	2	1.9
I21	Acute myocardial infarction	1	1.54	0	0.00	0	0.00	1	0.95
I38	Endocarditis, valve unspecified	1	1.54	0	0.00	0	0.00	1	0.95
I48	Atrial fibrillation and flutter	1	1.54	0	0.00	0	0.00	1	0.95
I49	Other cardiac arrhythmias	1	1.54	0	0.00	0	0.00	1	0.95
I63	Cerebral infarction	2	3.08	0	0.00	0	0.00	2	1.9
I71	Aortic aneurysm and dissection	1	1.54	1	2.56	0	0.00	2	1.9
I77	Other disorders of arteries and arterioles	0	0.00	1	2.56	0	0.00	1	0.95
J18	Pneumonia, organism unspecified	1	1.54	0	0.00	0	0.00	1	0.95
K25	Gastric ulcer	0	0.00	1	2.56	0	0.00	1	0.95
K55	Vascular disorders of intestine	0	0.00	2	5.13	0	0.00	2	1.9
K56	Paralytic ileus and intestinal obstruction without hernia	0	0.00	2	5.13	0	0.00	2	1.9
K57	Diverticular disease of intestine	2	3.08	0	0.00	0	0.00	2	1.9
K63	Other diseases of intestine	4	6.15	0	0.00	0	0.00	4	3.81
K74	Fibrosis and cirrhosis of liver	2	3.08	0	0.00	0	0.00	2	1.9
K81	Cholecystitis	0	0.00	1	2.56	0	0.00	1	0.95
M80	Osteoporosis with pathological fracture	0	0.00	1	2.56	0	0.00	1	0.95
N18	Chronic kidney disease	0	0.00	1	2.56	0	0.00	1	0.95
N19	Unspecified kidney failure	1	1.54	0	0.00	0	0.00	1	0.95
R54	Senility	1	1.54	0	0.00	0	0.00	1	0.95
R99	Other ill-defined and unspecified causes of mortality	1	1.54	0	0.00	0	0.00	1	0.95
S30-S39	Injuries to the abdomen, lower back, lumbar spine and pelvis	1	1.54	0	0.00	0	0.00	1	0.95
T66-T78	Other and unspecified effects of external causes	2	3.08	0	0.00	0	0.00	2	1.9
Total	Total	65		39		1		105	

4. Co-morbidities of Short Bowel Syndrome

I analyzed the co-morbidities accompanying SBS with any diagnostic codes in Table 40 which means even not recorded as a major primary code or the first four minor diagnostic codes, its diagnosis will be included. All the diagnostic codes that occurred before onset of SBS were excluded. Multiple co-morbidities were not mutually exclusive. Among the 168,475 co-morbidities, the diseases that most frequently accompanied SBS were gastritis and duodenitis (5.51%) followed by essential hypertension (4.84%), and other functional intestinal disorders (2.43%). The details with codes that occurred at a frequency ≥1% in patients with SBS were shown in Table 11.

Table 11 Most Common KCD Diagnosis Codes Associated With Short Bowel Syndrome

Code	Description	n	%
K29	GASTRITIS AND DUODENITIS	9,275	5.51
I10	ESSENTIAL(PRIMARY) HYPERTENSION	8,159	4.84
K59	OTHER FUNCTIONAL INTESTINAL DISORDERS	4,086	2.43
E11	NON-INSULIN-DEPENDENT DIABETES MELLITUS	3,936	2.34
M54	DORSALGIA	3,450	2.05
J20	ACUTE BRONCHITIS	3,327	1.97
J30	VASOMOTOR AND ALLERGIC RHINITIS	3,114	1.85
E78	DISORDERS OF LIPOPROTEIN METABOLISM AND OTHER LIPIDAEMIAS	2,435	1.45
N18	CHRONIC RENAL FAILURE	2,270	1.35
K21	GASTRO-OESOPHAGEAL REFLUX DISEASE	2,157	1.28
M17	GONARTHROSIS (ARTHROSIS OF KNEE)	2,097	1.24
K25	GASTRIC ULCER	2,000	1.19
K30	DYSPEPSIA	1,995	1.18
M79	OTHER SOFT TISSUE DISORDERS, NEC	1,773	1.05
K58	IRRITABLE BOWEL SYNDROME	1,686	1.00

Also for the comparison with non SBS patients, I analyzed co-morbidities with SBS underlying disease. Among the 21,285,552 co-morbidities, the diseases that most frequently accompanied SBS underlying disease were gastritis and duodenitis (6.63%) as same as SBS. Most of co-morbidities were similar however chronic renal failure was only shown in SBS co-morbidities (1.35%). The details with codes that occurred at a frequency ≥1% in patients with SBS underlying disease were shown in Table 12.

Table 12 Most Common KCD Diagnosis Codes Associated With Short Bowel Syndrome underlying disease

Code	Description	n	%
K29	GASTRITIS AND DUODENITIS	1,412,274	6.63
J30	VASOMOTOR AND ALLERGIC RHINITIS	803,691	3.78
I10	ESSENTIAL(PRIMARY) HYPERTENSION	795,794	3.74
J20	ACUTE BRONCHITIS	697,344	3.28
M54	DORSALGIA	505,735	2.38
E11	NON-INSULIN-DEPENDENT DIABETES MELLITUS	408,583	1.92
K59	OTHER FUNCTIONAL INTESTINAL DISORDERS	380,920	1.79
M17	GONARTHROSIS(ARTHROSIS OF KNEE)	376,725	1.77
J03	ACUTE TONSILLITIS	376,376	1.77
K30	DYSPEPSIA	358,691	1.69
E78	DISORDERS OF LIPOPROTEIN METABOLISM AND OTHER LIPIDAEMIAS	334,640	1.57
J06	ACUTE UPPER RESPIRATORY INFECTIONS OF MULTIPLE AND UNSPECIFIED SITES	306,066	1.44
K21	GASTRO-OESOPHAGEAL REFLUX DISEASE	303,001	1.42
M79	OTHER SOFT TISSUE DISORDERS, NEC	299,860	1.41
J45	ASTHMA	269,941	1.27
J00	ACUTE NASOPHARYNGITIS(COMMON COLD)	255,442	1.20
J02	ACUTE PHARYNGITIS	239,023	1.12
J01	ACUTE SINUSITIS	237,528	1.12
K58	IRRITABLE BOWEL SYNDROME	228,561	1.07
K25	GASTRIC ULCER	219,303	1.03

H10	CONJUNCTIVITIS	219,110	1.03
J04	ACUTE LARYNGITIS AND TRACHEITIS	214,002	1.01

5. Medical and Socioeconomic Burden of Short Bowel Syndrome

Among the total patients with SBS, all patients were treated upon admission. I analyzed all healthcare utilization related to SBS after onset of disease thus multiple healthcare utilization were not mutually exclusive. When categorized according to health care institution, the proportion of total SBS patients in primary clinics was 6.1% and that in referral centers, defined as general hospitals plus hospitals, was 90.9% and that in convalescent hospitals was 3.0%. The mean (±standard deviation) length of stay in clinics for any of outpatients and admission was 6.1 ± 13.2 days per year and that in hospitals was 63.1 ± 139.6 days. The mean (±standard deviation) length of stay in general hospitals was 80.2 ± 85.8 days per year and that in convalescent hospitals was the longest, 200.0 ± 401.9 days per year which means patients who are in convalescent hospitals spend more than half of year in hospitals. The detail number of patients and length of stay by year were shown in Table 13.

As mentioned in the method section, here the costs of SBS were defined only as direct costs, comprised of healthcare and pharmacy costs expended during two years after intestinal resection based on hypothesis that the medication costs were highest in the first two years after operation. If patients were dead before being two years after intestinal resection, the costs expended until the death were calculated. When period was calculated between operation and death among dead SBS patients, it was averagely 448 days supporting our hypothesis that is medication will focus on first two years after operation. Total expended healthcare costs among 344 SBS patients were 7,904,304,376

Korean won, consisting of 97% of total costs. Pharmacy costs were only 3% among SBS patients which means most of medication associated with SBS was treated in hospitals. The List of direct costs related to SBS by year were shown in the Table 14.

Table 13 Healthcare Utilization Related to Short Bowel Syndrome

	Type of healthcare institute			
	Clinics	Hospitals	General hospitals	Convalescent hospitals
No. of patients, n				
2002	8	0	33	0
2003	7	5	35	0
2004	5	5	42	0
2005	4	4	32	1
2006	6	8	55	0
2007	5	6	62	2
2008	5	11	63	3
2009	1	10	48	2
2010	2	12	68	2
2011	4	8	82	7
2012	1	6	82	7
2013	2	9	61	1
Length of stay, d (mean ± standard deviation)				
2002	2.8 ± 2.9	-	44.5 ± 28.4	-
2003	4.3 ± 5.5	32.6 ± 51.8	40.0 ± 25.5	-
2004	8.6 ± 9.2	19.2 ± 25.3	50.1 ± 53.3	-
2005	4.0 ± 6.0	41.8 ± 34.3	26.0 ± 19.9	1.0
2006	6.7 ± 4.8	36.8 ± 42.1	46.3 ± 31.5	-
2007	5.2 ± 8.8	7.3 ± 12.6	41.8 ± 35.8	77.0 ± 70.7
2008	1.8 ± 1.8	15.9 ± 31.7	29.7 ± 29.8	229.0 ± 198.8

2009	1.0	83.6 ± 120.9	53.9 ± 85.1	236.0 ± 182.4
2010	1.5 ± 0.7	48.3 ± 102.0	38.1 ± 43.8	201.5 ± 231.2
2011	1.8 ± 1.5	93.3 ± 67.3	41.2 ± 45.5	111.7 ± 132.1
2012	1.0	39.3 ± 48.4	33.2 ± 38.0	89.3 ± 109.3
2013	1.5 ± 0.7	29.1 ± 30.5	36.6 ± 42.0	76.0

Table 14 Direct Costs Related to Short Bowel Syndrome

SBS category	n	Medical costs*				
		Healthcare services		Pharmacy		Total
		Costs	%	Costs	%	Costs
Definite	6	209,742,060	97.7	4,924,380	2.3	214,666,440
Probable	119	3,467,107,126	98.4	57,578,439	1.6	3,524,685,565
Possible	219	4,227,455,112	95.8	185,987,623	4.2	4,413,442,735
Total	344	7,904,304,376	97.0	248,490,523	3.0	8,152,794,899

* Korean Won

Ⅳ. Discussion

In this thesis, I examined 47,406 SBS underlying disease carrying subjects who were extracted from a national database of 1,025,340 randomly selected subjects. I found overall prevalence of definite SBS was 1 per millions which is similar to other European countries. On the basis of probable and possible SBS, the prevalence is somewhat higher, 1-2 per hundred thousand. The tendency of prevalence of probable SBS seems slightly increasing from 2002 to 2013 however it is not possible to be seen in probable and definite SBS because of small number of patients. The overall incidence of SBS was estimated to be 0.00135 person-year and the incidence of definite SBS was 0.002344. The Kaplan-Meier curve of SBS by underlying disease confirmed that all SBS groups were associated with the highest risk in the congenital disease group. This finding indicates children associated with SBS may need more care.

In this cohort I use the operational definition of SBS because of no information regarding intestine length available in database. Especially patients with possible SBS defined as having SBS underlying disease and intestinal resection. Thus SBS patients may be overestimated compared to whole population. Despite of this over estimation problem, the prevalence and incidence of SBS in Korea were very low as already described in other data meaning SBS is ultra-rare disease.

The co-morbidities associated with SBS was shown that there is high risk of secondary complications such as other gastric disease, hypertension, diabetes mellitus, bronchitis and renal failure. Previous study reported that the most frequent complication associated with SBS is catheter-related infections because of long-term requirement of parenteral nutrition (Hartl, et al., 2009; Van Gossum, et al., 2001). This difference might be explained by the type of database used in the study. This is the claims data thus there may be a gap between real disease and diagnostic codes. However other co-morbidities

associated with SBS will aid to physicians to understand clinical course of SBS.

Data from the NHIS cohort databases also confirmed that SBS accounts for a substantial proportion of referral hospitals and SBS in Korea imposes a substantial medical and economic burden. Especially medical costs calculated here was only in two years or less if patients were dead before being two years after operation however it was 8,152,794,899 Korean Won from just 344 SBS patients. When seen in definite SBS patients, there was only 6 patients but total medical costs were 214,666,440 Korean Won. Because of imperfection of data, I did not calculate indirect costs in this study however most SBS patients require consistent parenteral nutrition which could be conducted in hospital mostly. Especially even though booming up the Nutrition Support Team in Hospitals after reimbursement of activity of 'Therapy by Nutrition Support Team' in August 2014, nutrition therapies in Korea still limited in hospitals rather than home differently to US and Europe. A survey showed that only 3 hospitals conducted home care services related to nutrition among 70 hospitals in Korea (Cho, et al., 2016). Thus most SBS patients may spend more time in hospitals for parenteral nutrition and it could be impose large loss of productivity. indirect costs associated with SBS might be very high.

This is the first nationwide population-based study on the epidemiology and burden of disease of SBS in Korea; nonetheless, it had several limitations. The most important limitation was that the diagnoses of SBS, underlying disease, or any other comorbidities were defined on the basis of KCD codes, which may be inaccurate compared with the diagnoses obtained from a medical chart, and underreporting of asymptomatic SBS or misclassification was also possible. Unfortunately, there had been no studies in terms of the validity of the medical insurance claims data for SBS in Korea. However, in terms of strokes and myocardial infarction have been validated in Korea using ICD codes. Park et

al showed that the accuracy rate of stroke diagnosis using KCD codes was 83.0% when defined cerebrovascular diseases as (1) the MONICA criteria; (2) the Minnesota Stroke Survey; or (3) CT and MRI findings (Park, et al., 2000). Also they showed in a same study that 10.0% of cases to be impossible to interpret because of insufficient records and 8.2% of cases to contain missing or unobtainable medical records, often due to hospital closures. Although other diseases can lead to acute myocardial infarction, the accuracy of diagnosing acute myocardial infarction using the ICD-10 codes in Korean Medical Insurance claims data were >70%, demonstrating a fair to good reliability. In addition, the NHIS confirmed that the prevalence of 20 major diseases for each year is similar to trends in the annual changes in NHIS-NSC 2002-2010 data validating the quality of the data. Also, to overcome this SBS diagnosis limitation, I considered SBS cases using combination of SBS diagnosis codes, operational codes and admission period. If there is large resection of colon and parenteral nutrition is required, patients will be admitted more than 1 month. Therefore, I think that definition of SBS diagnosis in this study is reliable but further study is needed to validate. Second, because I used administrative data, I could not obtain clinical activity, remnant length of colon, or laboratory findings, so I did not evaluate detailed clinical status or disease severity. Finally, because I could only obtain the medical costs covered by NHI, the uncovered medical costs did not be considered in this study.

Despite of these limitations, this population-based data provides better understanding of the epidemiology and burden of disease of patients associated with SBS. Also, a major strength of this study is the novel use of a nationwide database, which minimizes the effects of regional and population biases. Recently, government starts to expand the coverage of benefits to the rare disease however because of its rarity, few population-based studies have been performed regarding rare disease. Especially related to SBS, only few case reports were published in Korea. Thus, this study contributes novel data to

the field. The prevalence and incidence of SBS in Korea is quite low and has been stable in recent years. Of note, the Kaplan-Meier curve of SBS by underlying disease confirmed that all SBS groups were associated with the highest risk in the congenital disease group. This finding indicates children associated with SBS may need more care. In terms of burden of disease of SBS, data confirmed that SBS in Korea imposes a substantial medical and economic burden as well as the medical costs indicated tendency to increase during the last 12 years despite of low and stable prevalence. I hope this results will aid in future research and healthcare planning related to SBS or rare disease.

Ⅴ. Reference

Amiot, A., Messing, B., Corcos, O., Panis, Y., & Joly, F. (2013). Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. *Clinical nutrition, 32*(3), 368-374.

American Gastroenterological Association. (2003). American Gastroenterological Association medical position statement: short bowel syndrome and intestinal transplantation. *Gastroenterology*, *124*(4), 1105.

Bakker, H., Bozzetti, F., Staun, M., Leon-Sanz, M., Hebuterne, X., Pertkiewicz, M., ... & Thul, P. (1999). Home parenteral nutrition in adults: a european multicentre survey in 1997. ESPEN-Home Artificial Nutrition Working Group. *Clinical nutrition (Edinburgh, Scotland), 18*(3), 135-140.

Buchman, A. L., (2006). Etiology and initial management of short bowel syndrome. *Gastroenterology*, *130*(2 Suppl 1), S5-S15.

Buchman, A. L., Scolapio, J., & Fryer, J. (2003). AGA technical review on short bowel syndrome and intestinal transplantation. *Gastroenterology*, *124*(4), 1111-1134.

Buchman, A. L. (1997). The clinical management of short bowel syndrome: steps to avoid parenteral nutrition. *Nutrition, 13*(10), 907-913.

Canadian Collaborative Study Group Protocol: CAPS web page. Available at: *http://www.caps.ca.*

Cho J.Y., Kim J.T., Kim S.L., (2016). Survey on the state of nutrition support team (NST) activity: comparison of the questionnaire survey 2016 vs. 2005 and the State of NST activity since the introduction of the medical insurance fee. *Journal of the Korean Society for Parenteral and Enteral Nutrition, 8*(2), 38-44.

Cisler, J. J., & Buchman, A. L. (2005). Intestinal adaptation in short bowel syndrome. *Journal of investigative medicine, 53*(8), 402-413.

Cole, C. R., Hansen, N. I., Higgins, R. D., Ziegler, T. R., & Stoll, B. J. (2008). Very low birth weight preterm infants with surgical short bowel syndrome: incidence, morbidity and mortality, and growth outcomes at 18 to 22 months. *Pediatrics, 122*(3), e573-e582.

Dabney, A., Thompson, J., DiBaise, J., Sudan, D., & McBride, C. (2004). Short bowel syndrome after trauma. *The American journal of surgery, 188*(6), 792-795.

DiBaise, J. K., Young, R. J., & Vanderhoof, J. A. (2004). Intestinal rehabilitation and the short bowel syndrome: part 1. *The American journal of gastroenterology, 99*(7), 1386.

DiBaise, J. K., Young, R. J., & Vanderhoof, J. A. (2004). Intestinal rehabilitation and the short bowel syndrome: part 2. *The American journal of gastroenterology*, *99*(9), 1823.

Donohoe, C. L., & Reynolds, J. V. (2010). Short bowel syndrome. *The Surgeon, 8*(5), 270-279.

Forbes, A. (2014). Crohn's disease: Rehabilitation after resection. *Digestive Diseases*, 32(4), 395-398.

EMINET, (2011). Initial investigation to assess the feasibility of a coordinated system to access orphan medicines. Available at: *http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/access_orphans_initialinvest_052011_en.pdf.*

EUCERD, (2013). 2013 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE. Available at: *http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf.*

Hartl, W. H., Jauch, K. W., Parhofer, K., Rittler, P., & Working Group for Developing the Guidelines for Parenteral Nutrition of the German Association for Nutritional Medicine. (2009). Complications and monitoring–guidelines on parenteral nutrition, Chapter 11. *GMS German Medical Science, 7.*

Hofstetter, S., Stern, L., & Willet, J. (2013). Key issues in addressing the clinical and humanistic burden of short bowel syndrome in the US. *Current medical research and opinion, 29*(5), 495-504.

Howard, L., Ament, M., Fleming, C. R., Shike, M., & Steiger, E. (1995). Current use and clinical outcome of home parenteral and enteral nutrition therapies in the United States. *Gastroenterology, 109*(2), 355-365.

Jeppesen, P. B., & Mortensen, P. B. (2000). Intestinal failure defined by measurements of intestinal energy and wet weight absorption. *Gut, 46*(5), 701-706.

Jeppesen, P. B. (2014). Spectrum of short bowel syndrome in adults: intestinal insufficiency to intestinal failure. *Journal of Parenteral and Enteral Nutrition, 38*(1_suppl), 8S-13S.

Jung, H. K., Kim, Y. H., Park, J. Y., Jang, B. H., Park, S. Y., Nam, M. H., & Choi, M. G. (2014). Estimating the burden of irritable bowel syndrome: analysis of a nationwide korean database. *Journal of neurogastroenterology and motility, 20*(2), 242.

Keller, J., Panter, H. & Layer, P., (2004). Management of the short bowel syndrome after extensive small bowel resection. *Best Pract Res Clin Gastroenterol, 18*(5), 977-992.

Kelly, D. G., Tappenden, K. A., & Winkler, M. F. (2014). Short bowel syndrome: highlights of patient management, quality of life, and survival. *Journal of Parenteral and Enteral Nutrition, 38*(4), 427-437.

Kim, K. H. (2016). Comorbidity Adjustment in Health Insurance Claim Database. *Health Policy and Management, 26*(1), 71-78.

Kim, S. J., Kim, B. R., Lee, S. M., Kong, H. J., & Shin, C. S. (2013). Nutritional Support Process for a Patient with Short Bowel Syndrome in Conjunction with Panperitonitis: A Case

Report. *Clinical nutrition research, 2*(2), 149-153.

Koffeman, G. I., van Gemert, W. G., George, E. K., & Veenendaal, R. A. (2003). Classification, epidemiology and aetiology. *Best practice & research Clinical gastroenterology, 17*(6), 879-893.

Lal, S., Teubner, A., & Shaffer, J. L. (2006). intestinal failure. *Alimentary pharmacology & therapeutics, 24*(1), 19-31.

Lee, J., Lee, J. S., Park, S. H., Shin, S. A., & Kim, K. (2016). Cohort profile: The national health insurance service–national sample cohort (NHIS-NSC), South Korea. *International journal of epidemiology, 46*(2), e15-e15.

Matarese, L. E., Jeppesen, P. B., & O'Keefe, S. J. (2014). Short bowel syndrome in adults: the need for an interdisciplinary approach and coordinated care. *Journal of Parenteral and Enteral Nutrition*, *38*(1_suppl), 60S-64SWales, P. W., de Silva, N., Kim, J., Lecce, L., To, T., & Moore, A. (2004). Neonatal short bowel syndrome: population-based estimates of incidence and mortality rates. *Journal of pediatric surgery*, *39*(5), 690-695.

Messing, B., Crenn, P., Beau, P., Boutron-Ruault, M. C., Rambaud, J. C., & Matuchansky, C. (1999). Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. *Gastroenterology, 117*(5), 1043-1050.

Misiakos, E. P., Macheras, A., Kapetanakis, T., & Liakakos, T. (2007). Short bowel syndrome: current medical and surgical trends. *Journal of clinical gastroenterology, 41*(1), 5-18.

Mulcahy, V., & Forbes, A. (2015). Intestinal failure and short bowel syndrome. *Medicine, 43*(4), 239-243.

Nusinovich Y, Revenis M, Torres C. (2013). Long-term outcomes for infants with intestinal atresia studied at Children's National Medical Center. *J Pediatr Gastroenterol Nutr, 57*(3), 324-329.

Nightingale, J., & Woodward, J. M. (2006). Guidelines for management of patients with a short bowel. *Gut, 55*(suppl 4), iv1-iv12.

Official Journal of the European Communities, .., (1999). REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 1999 on orphan medicinal products.

Official Journal of the European Union, .., (2011). DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2011 on the application of patients' rights in cross-border healthcare.

O'Keefe, S. J., Buchman, A. L., Fishbein, T. M., Jeejeebhoy, K. N., Jeppesen, P. B., & Shaffer, J. (2006). Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clinical Gastroenterology and Hepatology, 4*(1), 6-10.

Orphanet, (2013). Prevalence of rare diseases: Bibliographic data. *Orphanet Report Series,* Volume Number 1.

Pant, C., Sferra, T. J., Fischer, R. T., Olyaee, M., & Gilroy, R. (2015). Epidemiology and healthcare resource utilization associated with children with short bowel syndrome in the United States. *Journal of Parenteral and Enteral Nutrition*, 0148607115616079.

Park, J. K., Kim, K. S., Kim, C. B., Lee, T. Y., Lee, K. S., Lee, D. H., ... & Ryu, S. Y. (2000). The accuracy of ICD codes for cerebrovascular diseases in medical insurance claims. *Korean Journal of Preventive Medicine, 33*(1), 76-82.

Parrish CR. (2005) The Clinician's Guide to Short Bowel Syndrome. *Practical Gastroenetrol. 31,* 67-106.

Pironi, L. (2016). Definitions of intestinal failure and the short bowel syndrome. *Best Practice & Research Clinical Gastroenterology, 30*(2), 173-185.

Pironi, L., Arends, J., Bozzetti, F., Cuerda, C., Gillanders, L., Jeppesen, P. B., ... & Szczepanek, K. (2016). ESPEN guidelines on chronic intestinal failure in adults. *Clinical Nutrition, 35*(2), 247-307.

Pironi, L., Arends, J., Baxter, J., Bozzetti, F., Peláez, R. B., Cuerda, C., ... & Jeppesen, P. B. (2015). ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. *Clinical Nutrition, 34*(2), 171-180.

Pironi, L., Goulet, O., Buchman, A., Messing, B., Gabe, S., Candusso, M., ... & Forbes, A. (2012). Outcome on home parenteral nutrition for benign intestinal failure: a review of the literature and benchmarking with the European prospective survey of ESPEN. *Clinical nutrition, 31*(6), 831-845.

Pironi, L., Hébuterne, X., Van Gossum, A., Messing, B., Lyszkowska, M., Colomb, V., ... & Bozzetti, F. (2006). Candidates for intestinal transplantation: a multicenter survey in Europe. *The American journal of gastroenterology, 101*(7), 1633.

Pironi, L., & Tognoni, G. (1995). Cost-benefit and cost-effectiveness analysis ofhome artificial nutrition: reappraisal of available data. *Clinical Nutrition, 14,* 87-91.

Rhoda, K. M., Parekh, N. R., Lennon, E., Shay-Downer, C., Quintini, C., Steiger, E., & Kirby, D. F. (2010). The multidisciplinary approach to the care of patients with intestinal failure at a tertiary care facility. *Nutrition in Clinical Practice*, *25*(2), 183-191.

Sanchez SE, McAteer JP, Goldin AB, Horslen S, Huebner CE, Javid PJ. (2013). Health-related quality of life in children with intestinal failure. *J Pediatr Gastroenterol Nutr, 57*(3), 330-334

Schalamon, J., Mayr, J. M., & Höllwarth, M. E. (2003). Mortality and economics in short bowel syndrome. *Best Practice & Research Clinical Gastroenterology, 17*(6), 931-942.

Smith, N., Harwood, R., & Almond, S. (2014). Short bowel syndrome–surgical perspectives and outcomes. *Paediatrics and Child Health, 24*(11), 513-518.

Song, J. Y., & Kim, H. Y. (2014). Nutrition Support for Pediatric Short Bowel Syndrome. *Journal of Clinical Nutrition, 6*(1), 19-23.

Staun, M., Hebuterne, X., Shaffer, J., Haderslev, K. V., Bozzetti, F., Pertkiewicz, M., ... & Pironi, L. (2007). Management of intestinal failure in Europe. A questionnaire based study on the incidence and management. *Dynamic Medicine, 6*(1), 7.

Storch, K. J. (2014). Overview of short bowel syndrome: clinical features, pathophysiology, impact, and management. *Journal of Parenteral and Enteral Nutrition*, *38*(1_suppl), 5S-7S.

Sundaram, A., Koutkia, P., & Apovian, C. M. (2002). Nutritional management of short bowel syndrome in adults. *Journal of clinical gastroenterology, 34*(3), 207-220.

Sulkowski, J. P., & Minneci, P. C. (2014). Management of short bowel syndrome. *Pathophysiology, 21*(1), 111-118.

Tappenden, K. A. (2014). Intestinal adaptation following resection. *Journal of Parenteral and Enteral Nutrition*, *38*(1_suppl), 23S-31S.

Thompson, J. S., Weseman, R., Rochling, F. A., & Mercer, D. F. (2011). Current management of the short bowel syndrome. *Surgical Clinics of North America, 91*(3), 493-510.

Thompson, J. S., DiBaise, J. K., Iyer, K. R., Yeats, M., & Sudan, D. L. (2005). Postoperative short bowel syndrome. *Journal of the American College of Surgeons, 201*(1), 85-89.

Van Gossum, A., Cabre, E., Hebuterne, X., Jeppesen, P., Krznaric, Z., Messing, B., ... & Nightingale, J. (2009). ESPEN guidelines on parenteral nutrition: gastroenterology. *Clinical nutrition*, *28*(4), 415-427.

Van Gossum, A., Vahedi, K., Staun, M., Pertkiewicz, M., Shaffer, J., Hebuterne, X., ... & Messing, B. (2001). Clinical, social and rehabilitation status of long-term home parenteral nutrition patients: results of a European multicentre survey. *Clinical nutrition, 20*(3), 205-210.

Van Gossum, A., Bakker, H., De Francesco, A., Ladefoged, K., Leon-Sanz, M., Messing, B., ... & Wood, S. (1996). Home parenteral nutrition in adults: a multicentre surveyin Europe in 1993. *Clinical nutrition, 15*(2), 53-59.

Vanderhoof, J. A., & Langnas, A. N. (1997). Short-bowel syndrome in children and adults. *Gastroenterology, 113*(5), 1767-1778.

Wales, P. W., de Silva, N., Kim, J., Lecce, L., To, T., & Moore, A. (2004). Neonatal short bowel syndrome: population-based estimates of incidence and mortality rates. *Journal of pediatric surgery, 39*(5), 690-695.

Wales, P. W., & Christison-Lagay, E. R. (2010). Short bowel syndrome: epidemiology and

etiology. In *Seminars in pediatric surgery, 19*(1), 3-9.

Wall, E. A. (2013). An overview of short bowel syndrome management: adherence, adaptation, and practical recommendations. *Journal of the Academy of Nutrition and Dietetics, 113*(9), 1200-1208.

Wilmore, D. W., Byrne, T. A., & Persinger, R. L. (1997). Short bowel syndrome: new therapeutic approaches. *Current problems in surgery, 34*(5), 389391-444.

Wong, T., & Gupte, G. (2015). Complications of short bowel syndrome. *Paediatrics and Child Health, 25*(9), 418-421.

국문 초록

한국에서의 단장증후군 환자 역학과 질병부담

조 연 경

서울대학교 보건대학원

보건학과 보건학전공

연구 배경/목적: 단장증후군의 유병률 및 질병부담에 대해 대규모 데이터를 이용한 연구가 부족한 실정이다. 본 연구에서는 2002-2013 년에 한번이라도 단장증후군 기저질환을 보유했던 국민건강보험공단 표본코호트를 이용하여, 단장증후군의 역학적 특징과 질병부담을 한국인을 대상으로 처음으로 분석하고자 한다.

연구 방법: 본 연구는 무작위로 추출된 1,025,340 명으로 이루어진 국민건강보험공단 표본코호트 데이터를 이용하였다. 이는 2002 년 자격이 충족된 한국인 가운데 2.2%이며, 해당 개인이 사망 또는 이민으로 자격이 상실되지 않을 경우 2013 년까지 12 년간 추적되었다. 단장증후군 환자는 진단 코드, 수술 코드와 입원 기간을 조합하여 확실한/그럴듯한/가능한 단장증후군, 세 그룹으로 조작적으로 정의하였다. 유병률과 발생률, 동반되는 다빈도 상병코드, 생존 분석, 질병 부담이 측정되었다.

연구 결과: 2002 년에서 2013 년 사이에 적어도 한 번 이상 단장증후군 기저질환을 보유한 47,406 명의 환자 중 총 344 명의 환자가 단장증후군 환자(가능한 단장증후군 219 명, 그럴듯한 단장증후군 119 명, 확실한 단장증후군 6 명)로 확인되었다. 단장증후군의 유병률은 십만 명당 2 ~ 3 명이었으며 발생률은 0.135 인년이었다. Kaplan-Meier 생존 곡선은 모든 단장증후군 그룹에서 선천적질환에서 질환 발생 위험이 가장 높음을 보여주었다. 단장증후군의 질병부담 측면에서는 낮은 유병률에도 불구하고 의료 및 경제적 부담이

상당하였음을 확인했다. 보건 의료 기관에 따라 분류했을 때, 의원에서는 전체 단장증후군 환자의 비율은 6.1 % 였고, 종합병원과 상급종합병원의 경우 90.9 % 였고, 요양병원의 경우 3.0 %였다. 외래 환자 및 입원 환자 중 의원에 머무르는 기간의 평균 (± 표준 편차)은 연간 6.1 ± 13.2 일이었고 종합병원에서는 평균 63.1 ± 139.6 일이었다. 상급종합병원의 평균 (± 표준 편차) 체류 기간은 80.2 ± 85.8 일이었고, 요양병원의 경우 200.0 ± 401.9 일로 가장 길었다.

결론: 단장증후군은 극희귀질환이지만, 질병과 연관된 복잡한 입원 과정과 높은 경제적 부담을 주는 질환이다. 이 연구는 국가 의료비 청구데이터를 이용하여 단장증후군과 관련된 역학 및 질병 부담을 분석한 첫 번째 연구이다.

주요어 : 단장증후군, 역학, 질병부담, 한국

학번 : 2015-24017